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RESEARCH ARTICLE

Age-specific outcomes from the first round of HPV screening in unvaccinated women: Observational study from the English cervical screening pilot

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Abstract

Objective: To report detailed age-specific outcomes from the first round of an English pilot studying the implementation of high-risk human papillomavirus (HR-HPV) testing in primary cervical screening.

Design: Observational study with screening in 2013–2016, followed by two early recalls and/or colposcopy until the end of 2019.

Setting: Six NHS laboratory sites.

Population: A total of 1 341 584 women undergoing screening with HR-HPV testing or liquid-based cytology (LBC).

Methods: Early recall tests and colposcopies were recommended, depending on the nature of the screening-detected abnormality.

Main outcome measures: We reported standard screening process indicators, e.g. proportions with an abnormality, including high-grade cervical intraepithelial neoplasia (CIN2+) or cancer, and the positive predictive value (PPV) of colposcopy for CIN2+, by screening test and age group.

Results: Among unvaccinated women screened with HR-HPV testing at age 24–29 years, 26.9% had a positive test and 10.4% were directly referred to colposcopy following cytology triage, with a PPV for CIN2+ of 47%. At 50–64 years of age, these proportions were much lower: 5.3%, 1.2% and 27%, respectively. The proportions of women testing positive for HR-HPV without cytological abnormalities, whose early recall HR-HPV tests returned negative results, were similar across the age spans: 54% at 24–29 years and 55% at 50–64 years. Two-thirds of infections at any age were linked to non-16/18 genotypes. Among women with CIN2, CIN3 or cervical cancer, however, the proportion of non-16/18 infections increased with age. As expected, the detection of abnormalities was lower following screening with LBC.

Conclusions: These data provide a reliable reference for future epidemiological studies, including those concerning the effectiveness of HPV vaccination.

Christopher S Mathews and Francesca Pesola contributed equally. Karin Denton and Henry Kitchener contributed equally.

Tweetable abstract: Data from the English pilot study provide a comprehensive overview of abnormalities detected through HPV screening.

KEYWORDS
Cervical cancer, human papillomavirus, outcomes, screening

1 | INTRODUCTION

The epidemiology of high-risk human papillomavirus (HR-HPV) infections has a very age-dependent pattern because the acquisition of new infections is most frequent at younger ages.[1] Some of the infections persist and can lead to the development of high-grade cervical intraepithelial neoplasia (CIN2+),[2,3] which may, usually over a period spanning longer than a decade, develop into cervical cancer in a relatively small proportion of women.[4–6] Consequently, the type and the frequency of screen-detected abnormalities vary with women's age.[7]

Vaccination against HPV16/18, the two genotypes that cause the majority of cases of cervical cancer,[8] is now changing these patterns.[9,10] At present, the largest decreases in the frequency of screen-detected abnormalities are being seen in the youngest women eligible for screening. Vaccination, however, is beginning to affect screening outcomes in somewhat older women not only because vaccination-eligible women are ageing but also because partial herd protection protects the unvaccinated.[11]

Observing and interpreting these age-specific trends in screen-detected abnormalities is one of the most cost-efficient and frequently employed methods to determine the population impact of HPV vaccination.[9,11–13] Such studies require that a pre-vaccination baseline, i.e. a description of vaccine-preventable abnormalities detected in women not eligible for vaccination, is established for all age groups. This is, however, becoming increasingly complicated because screening programmes started to replace cytology with HR-HPV testing around the time that vaccine-eligible birth cohorts began to fulfil the screening age criteria. As HR-HPV testing results in a higher detection of abnormalities across the entire age span,[14] historical data on vaccine-ineligible cohorts from the cytology screening era, even if recent, may be of limited use for the purpose.

We set out to establish a pre-vaccination baseline with age-specific and HR-HPV genotype-specific cervical screening outcomes for England, using data from a large HPV screening pilot embedded within the English Cervical Screening Programme (CSP) between 2013 and 2016.[14]

2 | METHODS

The CSP invites women every 3 years at age 25–49 years and every 5 years at age 50–64 years. The pilot, which has been described in detail previously,[14–16] used the same target age range and screening intervals. Briefly, the pilot was initiated in 2013 in six large liquid-based cytology (LBC) screening laboratories in Bristol, Liverpool, London (Northwick Park), Manchester, Norwich and Sheffield. These laboratories used ThinPrep (Hologic, Marlborough, MA, USA) and SurePath (Becton Dickinson, Franklin Lakes, NJ, USA) LBC systems, and cobas 4800 (Roche, Basel, Switzerland), APTIMA (Hologic) and RealTime (Abbott, Chicago, IL, USA) HR-HPV assays; a smaller number of women was screened using the Hybrid Capture 2 (Qiagen, Hilden, Germany) HR-HPV assay. Cobas and RealTime HR-HPV DNA genotyping assays report HPV genotypes 16 and 18 separately from the 12 other HR-HPV genotypes; the latter are reported in combination. The APTIMA HR-HPV mRNA assay detects the 14 HR-HPV genotypes in combination without a further breakdown by genotype. The pilot followed national screening and colposcopy quality assurance procedures.[17] All screening tests had been previously validated and are included in the list of approved technologies for the CSP.

Women screened with HR-HPV testing were directly referred to colposcopy if they tested positive for HR-HPV and had at least borderline cytological abnormalities in squamous or glandular cells. Women testing positive for HR-HPV with normal cytology were referred to early recall in 12 months and then returned to routine screening in the case of a negative HR-HPV test. In the case of persistently positive HR-HPV tests and incident cytological abnormalities, they were referred to colposcopy. At this 12-month early recall, three laboratory sites additionally referred to colposcopy cytology-negative women following persistently positive HR-HPV tests involving genotypes 16 and/or 18.[16] Other women with persistently positive HR-HPV tests and no cytological abnormalities were referred to a further early recall in another 12 months, when a referral to colposcopy was made in case of any persistently positive HR-HPV test, regardless of cytology. All triage cytology was read with the knowledge of the woman's HR-HPV infection. After the national roll-out, the CSP continued to use the same triage strategy but no longer employed genotyping at 12 months.[18]

For completeness, we also present outcomes from screening using LBC as the primary screening test. Women screened with LBC were referred to colposcopy if they had high-grade cytological abnormalities in squamous or glandular cells or low-grade (including borderline) abnormalities in combination with a positive HR-HPV triage test. In this case, cytology was read prior to HR-HPV testing.

Dates and diagnoses associated with HR-HPV tests, LBC and colposcopies within the pilot's prevalence-round episodes that started in 2013–2016 were retrieved directly from the laboratory information systems and were processed

centrally. Follow-up for these episodes was available until the end of 2019. We also retrieved data on CIN3 and cervical cancers from the English National Cancer Registration and Analysis Service (NCRAS) for the period 1995–2018,[19] using the unique NHS numbers for linkage. Throughout this article, data on CIN diagnoses detected within the pilot were based on laboratory sources, whereas the source of data on cervical cancers was NCRAS.

Individual-level data on the HPV vaccination status of the women were not available for analysis. Using national vaccination coverage data,[20] we estimated that 94% of the women screened in the pilot at age 24–29 years had not been vaccinated. The remaining 6% would have been eligible for a catch-up vaccination campaign, predominantly at ages 16–17 years. It is unlikely that older women undergoing screening in 2013–2016 had been vaccinated.[21,22]

For each woman, the first test within the prevalence round of the pilot was assumed to be the baseline screening test, unless the woman had had a cervical cancer diagnosis at any time, a CIN3 diagnosis in the preceding 3 years (as registered by the NCRAS), another screening test in the preceding 2 years or the test itself was described as having been made for follow-up to a previous abnormality.

2.1 | Statistical analysis

Age-specific outcomes reported separately for HR-HPV and LBC screening included the proportions of women with inadequate and positive screening tests referred to colposcopy at baseline, the positive predictive value (PPV) of a colposcopy for CIN2+ and CIN3+, and CIN2+ and CIN3+ detection per 1000 women screened. The same outcomes were also reported for the two early recalls after a baseline positive HR-HPV but negative cytology screen. As three laboratory sites piloted a scenario with an expedited colposcopy referral at the 12-month early recall,[16] the 24-month outcomes were based on data from the remaining three laboratory sites. Four sites reported HR-HPV genotyping data at the baseline screen, separately for genotypes 16 and 18, and for the 12 other high-risk genotypes in combination. Data from these four sites were used to determine the prevalence of infection in the baseline screening by genotype for all screened women, and then separately for women with cervical cancers, CIN3, CIN2 and <CIN2, detected at colposcopy following a positive HR-HPV screen. Finally, we determined the proportion of genotype-specific infections (16, 18 and other high-risk genotypes) in women with negative triage cytology that presented with a negative HR-HPV test at the 12-month early recall. HR-HPV genotypes were reported so that co-infections were grouped hierarchically: any genotype 16 infection, any genotype 18 infection without genotype 16 and any infection with the remaining 12 high-risk genotypes that did not involve genotypes 16 or 18. Simple counts of infections regardless of co-infections were reported in Appendix S1. In the main analysis, viral persistence at early recall was defined as the repeated detection of any HR-HPV; accordingly, viral clearance was defined as a negative early recall HR-HPV test after a previous positive HR-HPV test. Genotype-specific infections for women with persistently positive HR-HPV tests at the 12-month early recall were reported separately in Appendix S1.

All outcomes were stratified by age group (24–29, 30–39, 40–49 and 50–64 years). We included women aged 24 years because the first CSP screening invitation is sent at the age of 24.5 years. Additional breakdowns by 5-year age group were reported in Tables S1–S8, with the accompanying exact binomial 95% confidence intervals. Analyses were undertaken using R 3.6.1.

2.2 | Patient and public involvement

Neither patients nor the public were involved in the design or the management of this study.

3 | RESULTS

3.1 | Frequency of abnormalities on screening and early recall tests

In the pilot, 403 883 women were screened with HR-HPV testing and 937 701 women were screened with LBC (Table 1). The proportions of women with an initial invalid test were 0.2% with HR-HPV testing and 2.5% with LBC. The proportions of women with a positive screening test were substantially higher at younger ages. At age 24–29 years, 9.0% of those screened with LBC and 26.9% of those screened with HR-HPV testing had a positive result; at age 50–64 years, 1.1% screened positive on LBC and 5.3% screened positive on HR-HPV testing. The proportion of all screened women who tested positive for HR-HPV and had abnormalities on triage cytology decreased with age, from 10.4% at 24–29 years to 1.2% at 50–64 years. Among women with cytological abnormalities, the proportion with borderline abnormalities increased slightly with age, from 28.0% at 24–29 years to 36.8% at 50–64 years (Tables S1–S8). Consequently, the proportion directly referred to colposcopy among women with a positive HR-HPV test was about twice as high among younger women than it was among older women: 39% (10.4/26.9) at 24–29 years and 23% (1.2/5.3) at 50–64 years.

Of all women referred to the 12- and 24-month early recalls following an HR-HPV infection combined with negative cytology at baseline, around 85% attended each time; the differences by age were small.[15] Among women attending the 12-month early recall, 57.6% had persistently positive HR-HPV tests and 26.4% of those showed incident cytological abnormalities, leading to a referral to colposcopy (Table 2). Although the proportion of women with persistently positive HR-HPV tests did not vary substantially with age, older women were less likely to

TABLE 1 Testing outcomes at the baseline screening, by screening test and age group

Age group (years)	Number screened	Inadequate screening tests[a]	Positive screening tests	Direct referral to colposcopy[b]
HR-HPV testing				
24–29	76 277	197 (0.3%)	20 544 (26.9%)	7902 (10.4%)
30–39	108 363	299 (0.3%)	14 095 (13.0%)	4746 (4.4%)
40–49	116 037	268 (0.2%)	8468 (7.3%)	2306 (2.0%)
50–64	103 206	109 (0.1%)	5486 (5.3%)	1215 (1.2%)
Total	403 883	873 (0.2%)	48 593 (12.0%)	16 169 (4.0%)
LBC				
24–29	178 739	3894 (2.2%)	16 088 (9.0%)	16 088 (9.0%)
30–39	264 154	6564 (2.5%)	10 011 (3.8%)	10 011 (3.8%)
40–49	263 927	6119 (2.3%)	4859 (1.8%)	4859 (1.8%)
50–64	230 881	6910 (3.0%)	2551 (1.1%)	2551 (1.1%)
Total	937 701	23 487 (2.5%)	33 509 (3.6%)	33 509 (3.6%)

Abbreviations: HR-HPV, high-risk human papillomavirus; LBC, liquid-based cytology.

[a]The proportions were 0.09% for women screened with APTIMA, 0.03% for women screened with RealTime and 0.49% for women screened with cobas HR-HPV test assays, for all ages combined. For women screened with LBC, the proportions were 2.7% for SurePath and 2.3% for ThinPrep.

[b]Criteria for direct colposcopy referral: abnormalities of any grade in squamous or glandular cells on triage cytology after a positive HR-HPV screening test; with LBC screening, the threshold for referral was high-grade cytological abnormalities or low-grade (including borderline) abnormalities combined with a positive HR-HPV triage test.

develop incident cytological abnormalities than were younger women (30.2% at age 24–29 years versus 17.8% at 50–64 years). The pattern was similar at the 24-month early recall. Combining data from the two early recalls, we estimated that 56.9% of all women testing positive for HR-HPV but with negative cytology would present with a negative HR-HPV test within 24 months, suggesting viral clearance. This proportion was roughly similar across age groups (53.8% at 24–29 years, 58.4% at 30–39 years, 62.3% at 40–49 years and 54.5% at 50–64 years; not tabulated).

Overall, 6.5% of all women screened with HR-HPV testing were ultimately referred to colposcopy, including referrals at baseline and after early recall (Table 2), compared with 3.6% screened with LBC (Table 1). The proportion varied by age and was 15.7% at 24–29 years and 2.5% at 50–64 years with HR-HPV testing. About one-third (5.4/15.7) of all colposcopy referrals at age 24–29 years were made at early recall, compared with just over half (1.3/2.5) at age 50–64 years. Almost half of all colposcopy referrals within the programme (46%) were made at age 24–29 years (not tabulated). An additional 29% of colposcopy referrals were made at age 30–39 years, 15% at 40–49 years and 10% at 50–64 years.

3.2 | Positive predictive values of colposcopy

Following direct referral at baseline, the PPV of a colposcopy was identical for HR-HPV testing and LBC: 43% for CIN2+ and 27% for CIN3+ (Table 2). The PPV depended on the woman's age, even though the same colposcopy referral criteria were used across the age span. For CIN2+, the PPV decreased from 47% in women aged 24–29 years to 27% in women aged 50–64 years; the corresponding values for CIN3+ were 29% and 15%, respectively. At the 12-month early recall, among women with persistently positive HR-HPV tests in combination with incident abnormal cytology, the PPV for CIN2+ was 37% overall. At the 24-month early recall, when all women persistently testing positive for HR-HPV were referred to colposcopy, the PPV for CIN2+ was 21%. At that recall, 71% of referred women had negative cytology and their PPV for CIN2+ was 12% (Table S6). Early recall colposcopies continued to show a strong age gradient, approximately halving in values between the ages of 24–29 years and 50–64 years.

3.3 | Detection of CIN2+

With LBC as the primary screening test, 14.3 women per 1000 screened received a diagnosis of CIN2+, 9.2/1000 received a diagnosis of CIN3+ and 0.5/1000 received a diagnosis of cervical cancer (Table 3). As expected, the overall detection, including detection at baseline and the two early recalls, was higher with HR-HPV testing than with LBC, 22.9/1000 for CIN2+, 13.8/1000 for CIN3+ and 0.7/1000 for cervical cancer, owing to increases observed in all age groups. HR-HPV testing detected about 10% more lesions following the direct colposcopy referral (e.g. for CIN2+: 16.4/14.3). About a quarter of all CIN2+ and CIN3+ were detected during early recall, slightly more at 12 than at 24 months. The detection of all lesions including cervical cancer decreased with women's age. At 24–29 years, 63.9/1000 women had a CIN2+ diagnosis after a positive HR-HPV screen, whereas at 50–64 years the detection rate was 5.0/1000 women screened. This means

TABLE 2 Outcomes of HR-HPV testing at baseline and the two early recalls, by age group

			Early referral outcomes[b]				PPV of colposcopy[b]		
Age group (years)	Colposcopy referral[a]	Early recall referral[a]	Attended	HR-HPV positive	HR-HPV positive and negative LBC[c]	HR-HPV positive and abnormal LBC[c]	Attended	CIN2+ (PPV for CIN2+)[d]	CIN3+ (PPV for CIN3+)[d]
Baseline (direct)									
24–29 years	7902 (10.4%)	12 568 (16.5%)	NR	NR	NR	NR	7569	3522 (47%)	2208 (29%)
30–39 years	4746 (4.4%)	9282 (8.6%)	NR	NR	NR	NR	4558	2053 (45%)	1336 (29%)
40–49 years	2306 (2.0%)	6123 (5.3%)	NR	NR	NR	NR	2226	722 (32%)	448 (20%)
50–64 years	1215 (1.2%)	4328 (4.1%)	NR	NR	NR	NR	1150	312 (27%)	176 (15%)
Total	16 169 (4.0%)	32 211 (8.0%)	NR	NR	NR	NR	15 503	6609 (43%)	4168 (27%)
12-month early recall									
24–29 years	1964 (2.6%)	4504 (5.9%)	10 596	6505 (61.4%)	4504 (69.2%)	1964 (30.2%)	1860	785 (42%)	446 (24%)
30–39 years	1202 (1.1%)	3243 (3.0%)	7978	4482 (56.2%)	3243 (72.4%)	1202 (26.8%)	1142	430 (38%)	268 (23%)
40–49 years	663 (0.6%)	2110 (1.8%)	5448	2787 (51.2%)	2110 (75.7%)	663 (23.8%)	629	175 (28%)	85 (14%)
50–64 years	394 (0.4%)	1807 (1.8%)	3756	2219 (59.1%)	1807 (81.4%)	394 (17.8%)	363	93 (26%)	53 (15%)
Total	4223 (1.0%)	11 664 (2.9%)	27 778	15 993 (57.6%)	11 664 (72.9%)	4223 (26.4%)	3994	1483 (37%)	852 (21%)
24-month early recall									
24–29	699 (2.8%)	NR	1088	699 (64.2%)	452 (64.7%)	242 (34.6%)	647	186 (29%)	97 (15%)
30–39	493 (1.4%)	NR	768	493 (64.2%)	340 (69.0%)	148 (30.0%)	470	102 (22%)	47 (10%)
40–49	309 (0.9%)	NR	473	309 (65.3%)	241 (78.0%)	66 (21.4%)	285	34 (12%)	14 (5%)
50–64	274 (0.9%)	NR	382	274 (71.7%)	233 (85.0%)	39 (14.2%)	257	33 (13%)	16 (6%)
Total	1775 (1.4%)	NR	2711	1775 (65.5%)	1266 (71.3%)	495 (27.9%)	1659	355 (21%)	174 (10%)

Note: The proportion of all women testing positive for HR-HPV with negative cytology who present with a negative HR-HPV test within 24 months was estimated at 56.9% ((100%–57.6% [women who were HR-HPV positive and cytology negative at baseline and had a negative HR-HPV test by 12 months]) + 57.6% × 72.9% × (100%–65.5%) [women who were HR-HPV positive and cytology negative at baseline but had persistently HR-HPV positive tests and persistently negative cytology at 12 months and a negative HR-HPV test by 24 months]). We assumed that women who did not attend early recall were similar to women who did.

Abbreviations: CIN, cervical intraepithelial neoplasia; HR-HPV, high-risk human papillomavirus; LBC, liquid-based cytology; NR, not relevant; PPV, positive predictive value of a colposcopy.

[a]Columns with direct referral to colposcopy and to 12-month early recall do not add up to the number of all women with a positive HR-HPV test because of a small number of inadequate or missing triage LBC results. Denominator at baseline and the 12-month recall: all women screened with HR-HPV testing in the pilot. Denominator at the 24-month recall: women screened with HR-HPV testing in the three pilot sites that did not use HPV16/18 genotyping for triage at the 12-month early recall. The three sites provided HR-HPV screening to 124 058 women out of 403 883 women in the entire pilot.

[b]Data for 24-month early recall include three laboratory sites that did not manage women according to HR-HPV genotype at the 12-month early recall.

[c]The sum of the two columns is not the same as the number of women testing positive for HR-HPV because of a small number of inadequate or missing LBC results.

[d]Baseline PPV for CIN2+ with LBC as the primary screening test: 46% at 24–29 years, 44% at 30–39 years, 35% at 40–49 years, 28% at 50–64 years and 43% overall (24–64 years). Baseline PPV for CIN3+ with LBC as the primary screening test: 30%, 29%, 21%, 17% and 27%, respectively.

TABLE 3 Numbers of women with CIN2+, CIN3+, and cervical cancer per 1000 screened detected after a positive screening test, by screening test, age, and triage outcomes

	CIN2+				
	HR-HPV testing				LBC
	Direct (baseline) (per 1000)[a]	12-month early recall (per 1000)[a]	24-month early recall (per 1000)[b]	Total per 1000[c]	Total per 1000[a]
Age group (years)					
24–29	3522 (46.2)	785 (10.3)	186 (7.4)	63.9	7024 (39.3)
30–39	2053 (18.9)	430 (4.0)	102 (3.0)	25.9	4085 (15.5)
40–49	722 (6.2)	175 (1.5)	34 (1.0)	8.7	1609 (6.1)
50–64	312 (3.0)	93 (0.9)	33 (1.1)	5.0	667 (2.9)
Total	6609 (16.4)	1483 (3.7)	355 (2.9)	22.9	13 385 (14.3)

Abbreviations: CIN, cervical intraepithelial neoplasia.

[a]Denominator: all women screened in the pilot, with the respective screening test.

[b]Denominator: women screened in the three pilot sites that did not use HPV16/18 genotyping for triage at the 12-month early recall. The three sites provided HR-HPV screening to 124 058 women, out of 403 883 in the entire pilot.

[c]Calculated as the sum of proportions after direct colposcopy referral at baseline and after early recall.

[d]Absolute numbers not shown to reduce the risk of re-identification.[41]

that about a quarter (63.9/269) of all women who screened positive for HR-HPV at 24–29 years had a CIN2+ diagnosis, whereas this rate was only around 10% (5.0/53) in women aged 50–64 years.

3.4 | Genotype-specific infections

Among women with a positive HR-HPV screening test at any age, about two-thirds had only non-16/18 infections; about a quarter had HPV16 infections with or without co-infections, and fewer than 10% had HPV18 infections with or without co-infections with genotypes other than HPV16 (Table 4). HPV16/18 infections were slightly less likely to be followed by a negative HR-HPV test within 12 months than were non-16/18 high-risk infections. Older women were slightly more likely to have a negative HR-HPV test at the 12-month early recall following baseline HPV16/18 infections than younger women (34% at 40–64 years versus 26% at 24–29 years for HPV16 with or without any other high-risk infections, and 46% versus 32%, respectively, for HPV18 with or without any non-HPV16 high-risk infections). More detailed genotyping data showed that at any age by far the majority of infections detected at the 12-month early recall involved the same genotypes as infections detected at baseline, suggesting a high likelihood that these were true persisting infections (Table S9).

The largest proportion of women with screen-detected cancer were infected with HPV16; however, this proportion decreased with age, whereas the proportion infected with non-16/18 high-risk genotypes increased. The increasing presence of non-16/18 genotypes with age could also be observed with CIN2 and CIN3. The PPV for CIN2+ was much higher for HPV16/18 infections than for infections with other high-risk genotypes, but decreased with age regardless of the genotype group (Table S8).

4 | DISCUSSION

4.1 | Main findings

These data provide a pre-vaccination baseline for England, detailing epidemiological outcomes that are typically monitored in cervical screening. Importantly, they were derived from an early implementation of HR-HPV testing in diverse areas across England before the screening programme encompassed vaccination-eligible cohorts. As the detection of infections differs by HR-HPV assay,[23] we must emphasise, furthermore, that the pilot used the same clinically validated HR-HPV assays that continue to be used after the national roll-out. This should facilitate the interpretation of the results from future studies using routinely collected primary screening data. Previously, a UK-wide HR-HPV genotype pre-vaccination baseline was established for cases of CIN3 and cervical cancer.[24] Although several countries have published their pre-vaccination baselines,[11,25–29] those often focused on a limited number of end points from cytology-based screening or had to rely on small numbers of samples tested for HR-HPV, sometimes from selected populations.

4.2 | Interpretation (in light of other evidence)

Close to half of all colposcopies in the CSP were made in young women, and these colposcopies had a high yield of CIN2+. Furthermore, more women screened in their 20s received a diagnosis of a screen-detected cancer than did women who were screened in their 40s or later (1.1/1000 versus 0.5/1000). This is perhaps surprising given that untreated CIN2/3 lesions are less likely to progress to cervical cancer at younger compared with older ages,[6,30–32] but the observation

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CIN3+					Cervical cancer[d]	
HR-HPV testing				LBC	HR-HPV testing	LBC
Direct (baseline) (per 1000)[a]	12-month early recall (per 1000)[a]	24-month early recall (per 1000)[b]	Total per 1000[c]	Total per 1000[a]	Total per 1000[a,c]	Total per 1000[a]
2208 (28.9)	446 (5.8)	97 (3.9)	38.7	4545 (25.4)	1.1	0.7
1336 (12.3)	268 (2.5)	47 (1.4)	16.2	2679 (10.1)	0.9	0.7
448 (3.9)	85 (0.7)	14 (0.4)	5.0	963 (3.6)	0.5	0.4
176 (1.7)	53 (0.5)	16 (0.5)	2.8	393 (1.7)	0.4	0.2
4168 (10.3)	852 (2.1)	174 (1.4)	13.8	8580 (9.2)	0.7	0.5

could be partly explained as an effect of previous screening rounds in older women. HPV16/18 infections usually show a more rapid progression to high-grade CIN than other high-risk infections.[33] Previous screening, with participation rates above 70%,[34,35] are likely to have removed a significant proportion of CIN2/3 lesions that developed early after an HPV16/18 infection, and contributed to the observation in this as well as in previous studies that the proportion of CIN2+ associated with HPV16/18 decreases with age.[29,36]

The PPV associated with HPV16/18 is highly dependent on the cytology status, which, following primary HR-HPV testing, is the driver of colposcopy referral in the English programme. Our data have shown that amongst women with positive HR-HPV testing and abnormal cytology, the PPV for colposcopy detection of high-grade CIN was around 40%, at both baseline referral and early recall, similar to that seen using LBC as the primary screen with HR-HPV triage. Although there were some differences between groups with different genotypes, the PPV for those with non-16 and non-18 HR-HPV was still around 30%. The small proportion of women (about one in six) who were referred because of persistent HR-HPV after 24 months of negative cytology had a PPV of around 12%. Although the subgroup of HPV16/18 positives in this cohort might have a higher PPV, it would seem unlikely that knowledge of this at the time of colposcopy would facilitate significantly higher colposcopic performance, but it would add complexity. Prospective studies designed to address the value of knowing the genotype at colposcopy, amongst women with persistently negative cytology, would be required to gain reliable insight.

These data, confirming that HPV16/18 are implicated in most screen-detected abnormalities in unvaccinated women, suggest that the pressure on colposcopy services may diminish progressively amongst women who have entered the CSP in England since 2020, which is the time point marking the start of screening eligibility for cohorts offered vaccination in the comprehensive national school-based HPV vaccination programme at age 12–13 years. The average PPV of the remaining colposcopies in the CSP will however fall. The literature showed that the PPV of colposcopy is lower in women from the vaccinated cohorts.[37,38] We also showed here that the PPV is substantially lower in older women. The data, therefore, highlight that the referral threshold may need to be reconsidered if the PPV of colposcopy is to maintain its current levels of performance. Moreover, vaccination will require other profound changes to the CSP in order to maintain the cost-effectiveness of screening. In light of a diminishing risk of cervical cancer, the screening frequency of vaccine-eligible cohorts will need to be de-intensified, possibly requiring an increase in the screening entry age criteria.[39]

4.3 | Strengths and limitations

The principal strength of these data is the large size of the cohort, including women from different areas across England. The screening followed CSP quality assurance standards and women testing positive for HR-HPV were managed according to the same clinical protocols as have been in place within the programme after the national roll-out, since December 2019. A relative weakness of the pilot was that the allocation of HR-HPV tests and LBC was not randomised at an individual level. Previous analyses comparing the outcomes of the two screening tests were adjusted for the woman's age and deprivation score, which hardly changed the point estimates determined through direct comparison of the two screening tests.[14] Finally, the reported data are not representative of women screened with HR-HPV testing more than once. The second and later rounds of screening with HR-HPV testing

TABLE 4 Genotype-specific infections in the whole screened population and in women with screen-detected lesions. Based on four laboratory sites that reported genotype-specific data ($N = 311\,933$)

	HR-HPV infections				Lesions detected following a positive HR-HPV test			
Genotype	HR-HPV+ (95% CI)[a]	HR-HPV+/ cytology– (95% CI)[a]	Persisted (95% CI)[b]	Cleared (95% CI)[b]	Cervical cancer (95% CI)[c,d]	CIN3 (95% CI)[c]	CIN2 (95% CI)[c]	<CIN2 (95% CI)[c]
24–29 years								
Total	15 200	9391	4984	3001	61	2140	1392	5448
HPV16	8% (7–8)	4% (3–4)	74% (72–76)	26% (24–28)	66% (52–77)	57% (55–60)	41% (38–43)	26% (25–27)
HPV18	2% (2–2)	1% (1–1)	68% (64–72)	32% (28–36)	16% (8–28)	7% (6–8)	9% (7–10)	8% (7–9)
Other high-risk HPV	17% (17–18)	12% (12–12)	58% (57–60)	42% (40–43)	18% (9–30)	35% (33–37)	50% (48–53)	66% (64–67)
30–39 years								
Total	10 477	7011	3525	2568	75	1240	739	3695
HPV16	3% (3–3)	2% (2–2)	70% (67–72)	30% (28–33)	60% (48–71)	48% (45–50)	33% (30–37)	24% (23–26)
HPV18	1% (1–1)	1% (1–1)	60% (56–65)	40% (35–44)	23% (14–34)	8% (6–9)	10% (8–12)	8% (7–9)
Other high-risk HPV	9% (8–9)	6% (6–6)	55% (53–56)	45% (44–47)	17% (10–28)	44% (41–47)	57% (53–60)	67% (66–69)
40–64 years								
Total	11 009	8276	4194	3174	73	619	487	4223
HPV16	1% (1–1)	1% (1–1)	66% (63–69)	34% (31–37)	49% (37–61)	41% (37–45)	29% (25–34)	22% (21–23)
HPV18	<1% (<1–<1)	<1% (<1–<1)	54% (49–59)	46% (41–51)	14% (7–24)	9% (7–12)	7% (5–9)	7% (6–8)
Other high-risk HPV	5% (5–5)	4% (4–4)	55% (54–56)	45% (44–46)	37% (26–49)	50% (46–54)	63% (59–68)	70% (69–72)
24–64 years								
Total	36 686	24 678	12 703	8743	209	3999	2618	13 366
HPV16	3% (3–3)	2% (2–2)	70% (69–72)	30% (28–31)	58% (51–65)	52% (50–53)	36% (35–38)	24% (24–25)
HPV18	1% (1–1)	<1% (<1–<1)	61% (59–64)	39% (36–41)	18% (13–24)	8% (7–8)	9% (8–10)	8% (7–8)
Other high-risk HPV	8% (8–8)	6% (6–6)	56% (55–57)	44% (43–45)	24% (19–31)	40% (39–42)	55% (53–57)	68% (67–68)

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; HR-HPV, human papillomavirus.

Genotypes are reported so that co-infections were grouped hierarchically: any genotype 16 > any genotype 18 > any of the 12 other high-risk genotypes in combination. Ages 40–64 are grouped because of small numbers in some of the cells.

[a]At baseline. Denominator: all screened women.

[b]HR-HPV positive ("persistence") or negative ("clearance") at the 12-month early recall. Denominator: women who attended the 12-month early recall, by genotype.

[c]Detected at colposcopy at baseline or at any early recall. Denominator: all lesions of a specific grade.

[d]Detection of cervical cancers related to HPV16/18 infections, per 1000 screened women: 0.9/1000 at 24–29 years, 0.8/1000 at 30–39 years, and 0.3/1000 at 40–64 years. Detection of cervical cancers related to non-16/18 high-risk HPV infections, per 1000 screened women: 0.2, 0.2, and 0.2, respectively.

are expected to result in a lower detection of abnormalities than the first.[14,40] The follow-up with two early recalls in the second round of the pilot is not yet complete, particularly for older women whose routine recall was every 5 years.

5 | CONCLUSION

These data, with a detailed account of cervical screening outcomes using HR-HPV testing in an unvaccinated population, can be expected to provide a reliable baseline for understanding the impact of HPV16/18 vaccination on both the outcomes and clinical performance of screening.

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CONFLICT OF INTEREST

MR: Public Health England provided the financing for the epidemiological evaluation of the pilot and another study related to HPV detection; member of the Public Health England Laboratory Technology Group and HPV Self-sampling Operational Steering Group and Project Board; attended meetings with various HPV assay manufacturers; fee for lecture from Hologic paid to employer. CM: held an honorary appointment at Public Health England to process the data for the pilot. FP: no conflict of interest. KC: research funding or consumables to support research in the last 3 years from Cepheid, Euroimmun, GeneFirst, SelfScreen, Hiantis, Seegene, Roche, Abbott and Hologic, paid to employer; professional clinical advisor to Public Health England; member of Laboratory Technology Group and HPV Self-sampling Operational Steering Group. KD: adviser to Public Health England (this position is funded by Public Health England as a secondment from her main employment); chair of the Public Health England Laboratory Clinical professional group, the HPV development group and several groups related to the evaluation of self-sampling; consultant to the Scally Review of cervical screening in Ireland and the Royal College of Obstetricians and Gynaecologists review of cervical cancer audit in Ireland, both completed in 2019; expert medicolegal reports prepared for claimants and defendants, including in cases of cervical cancer; received support with travel expenses to attend an international meeting in May 2019 from Hologic, a company manufacturing equipment and consumables for cytology and HPV testing. HK: former chair of the Public Health England Advisory Committee for Cervical Screening. The views expressed in this article are those of the authors and do not represent the views of Public Health England. Completed disclosure of interests form available to view online as supporting information.

AUTHOR CONTRIBUTIONS

Study conception (the pilot study): the pilot steering group. Study conception (this article): MR. Data management: CM. Statistical analysis: MR and FP. Writing (original draft): MR. Writing (review and editing): all authors. Decision to submit: all authors.

ETHICS APPROVAL

The study was considered the first stage in national implementation, so it was referred to as an implementation pilot and therefore was exempt from ethics approval. Women participating in the HPV primary screening pilot were invited to make an informed choice on participating in the cervical screening programme. A decision is made to accept or decline a screening test based on access to accurate and up-to-date information on the condition being screened for, the testing process and the potential outcomes. Specific information was provided at the invitation stage allowing for personalised informed choice. There was further opportunity to reflect on what the test and its results might mean when they attended for screening with the clinician taking the sample. Regulation 5, Health Service Regulations 2002, Confidentiality Advisory Group ref. 15/CAG/0207, was the legal basis for processing the data.

DATA AVAILABILITY STATEMENT

The data belong to the former Public Health England and the authors cannot provide access to the relevant data sets to third parties. Requests for data and pre-application advice should instead be made to Office for Data Release (ODR@phe.gov.uk).

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SUPPORTING INFORMATION

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